RESPONSE

Claims 12-19 remain in the Application. Claims 12, 17, and 19 are in independent form. Claim 19 is a new claim that is clearly supported by the specification.

The instant specification is objected to for the incorrect use of the following trademarks: "TWEEN 80™" and "SPAN 80™." Applicants have made the appropriate changes throughout the entire specification in compliance with the Examiner's suggestion and M.P.E.P. 608.01(V). Reconsideration of the objection is respectfully requested.

Additionally, the specification is objected to because of the meaning of the recitation "$40.9°C." Applicants have amended the recitation to "40.9°C." Reconsideration of the objection is respectfully requested.

Claims 12, 13, 16, and 17 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Sato et al. According to the Office Action, Sato et al. teaches an antigenic composition comprising a culture filtrate antigen of *Erysipelothrix rhusiopathiae* culture (i.e., fluid fraction) that is mixed with aluminum phosphate gels. Further, the antigen fraction is mixed with Freund's complete adjuvant. The office action states that the aluminum phosphate gel is added as a stabilizing agent.

In response thereto, Applicants' argument is twofold. First, the aluminum phosphate gel used in the preparation of the immunogen of the Sato et al. reference is not added as a stabilizing agent. Instead, the aluminum phosphate gel is added as an adjuvant. Aluminum phosphate gel has been used as an adjuvant since the 1920s and is one of the only adjuvants approved by the FDA for use in licensed human vaccines (See, http://scharp.org/public/redbook/protocol/015.htm). According to Sato et al., the fractions from the culture supernatant were mixed with the aluminum phosphate gels in order to test for immunogenicity of the fractions (See, Section Title). In other words, the aluminum phosphate gels are added to the fractions to increase the intensity of the immune response (i.e., as an adjuvant). In contradistinction, the present invention utilizes, *inter alia*, aluminum phosphate gel as a stabilizing agent in order to "maintain the antigenic potential of a fluid fraction of an *E. rhusiopathiae* culture or otherwise slow the degradation of its antigenic potential after removal of the bacteria." (Page 6, Lines 9-11 of the Specification). Absent a showing in the prior art that aluminum phosphate gels are used as stabilizing agents, the only use of aluminum phosphate gels known to those of skill in the art is for adjuvant purposes. Thus, the use of aluminum phosphate gel as a

stabilizing agent as opposed to an adjuvant, as claimed in the present application, provides for a patentable distinction over the prior art.

Second, the Sato et al. reference teaches the addition of the aluminum phosphate gels long after obtaining the fluid fractions of the *E. rhusiopathiae* culture. It is well known in the art that adjuvants are added to vaccine compositions a long period of time after obtaining the fluid fractions. Thus, absent a showing to the contrary, Sato et al. teaches the addition of the aluminum phosphate gels to the fluid fractions of the *E. rhusiopathiae* culture after a long period of time. In contradistinction, the present invention provides for the addition of the stabilizing agent (e.g., aluminum phosphate gel, calcium phosphate gel, etc.) immediately after the supernatant fraction is taken from the fluid fraction of the *E. rhusiopathiae* culture. This provides for immediate hindrance of the degradation of the antigenic potential of the *E. rhusiopathiae* culture. Because the aluminum phosphate gel taught by the present invention is used as a stabilizing agent as opposed to an adjuvant, the presently pending claims are patentably distinct over the prior art. Thus, reconsideration of the rejection is respectfully requested.

Claims 12 and 14-16 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Sawada et al. According to the Office Action, Sawada et al. teaches an antigenic composition comprising a supernatant fluid (i.e., fluid fraction) obtained from an *Erysipelothrix rhusiopathiae* culture that is inactivated with formalin. The Office Action further states that the formalin acts as a stabilizing agent or preservative.

The formalin is used, however, for killing the *E. rhusiopathiae* bacteria and not as a stabilizing agent. In the Office Action, the terms "stabilizing agent" and preservative are used interchangeably. Unfortunately, these terms are, by definition, completely different from each other. A preservative is a "substance or preparation added to a product for the purpose of destroying or inhibiting the multiplication of microorganisms" (See, Dorland's Illustrated Medical Dictionary, p. 1254, Twenty Fifth Ed., 1974)(See also, *Wood RL*, which states that the use of a bacterin consisting of formalin-killed whole culture adsorbed on aluminum hydroxide gel was first reported in East Germany in 1947, *J.Am.Vet.Med.Assoc.* 184: 948, 944-949, 1984). On the other hand, a stabilizing agent is an agent used to "maintain the antigenic potential of a fluid fraction of an *E. rhusiopathiae* culture or otherwise slow the degradation of its antigenic potential after removal of the bacteria." (Page 6, Lines 9-11 of the Specification). Thus, the formalin used by Sawada et al. is not a stabilizing agent as disclosed and claimed by the present application. Even the Oaks et al. reference teaches the use of formalin as only a

common preservative and not as a stabilizing agent in antigen or vaccine compositions. Therefore, the disclosure of Sawada et al. does not anticipate the presently pending claims of the present application. Reconsideration of the rejection is respectfully requested.

Claims 12, 17, and 18 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Dayalu et al. in view of Sato et al., and Wild R.L. As stated in the Office Action, Dayalu et al. discloses a vaccine composition comprising an *E. rhusiopathiae* antigen extract and merthiolate as a preservative. Further, Dayalu et al. is silent about whether or not the antigen extract is a fluid fraction from *E. rhusiopathiae* culture. As for the Wild RL reference, the Office Action states that it teaches most of the immunizing antigen that is found in the *E. rhusiopathiae* culture. The Office Action states that it would have been obvious to one of ordinary skill in the art at the time the invention was made to replace the *E. rhusiopathiae* antigen extract in Dayalu's vaccine composition with Sato et al.'s culture filtrate antigen of *E. rhusiopathiae* culture to produce the vaccine composition of the instant invention with a reasonable expectation of success. "One skilled in the art would have been motivated to produce the instant invention for the expected benefit of providing, advantageously, a vaccine composition that comprises most of the immunizing antigen of *E. rhusiopathiae* as taught by Wild. Substituting one antigenic composition in a vaccine with another, alternative, art-known antigenic composition that comprises most of the immunizing antigen of *E. rhusiopathiae* would have been obvious to one skilled in the art." (Page 5, Paragraph 6).

In response thereto, Applicants first require clarification of the Wild RL reference. The citation provided by the Office Action is for a reference to "Wood RL" and not "Wild RL." Clarification is respectfully requested.

As previously discussed, the present invention is clearly patentably distinct from the antigen/vaccine composition disclosed by Sato et al. Further, MERTHIOLATE™, which is a trademark for thimerosal, is defined as an effective antiseptic against pathogenic microorganisms. It is thus a preservative as opposed to a stabilizing agent. As previously defined above, a preservative is a "substance or preparation added to a product for the purpose of destroying or inhibiting the multiplication of microorganisms" (See, Dorland's Illustrated Medical Dictionary, p. 1254, Twenty Fifth Ed., 1974). On the other hand, a stabilizing agent is an agent used to "maintain the antigenic potential of a fluid fraction of an *E. rhusiopathiae* culture or otherwise slow the degradation of its antigenic potential after removal of the bacteria." (Page 6, Lines 9-11 of the

Specification). Therefore, the presently claimed antigen and vaccine compositions of the present invention are clearly different from the vaccine composition taught by Dayalu et al.

In view of the above, the presently pending claims are not anticipated by the prior art. Further, there is no suggestion in the prior art references themselves to combine the teachings of those references, nor is there any motivation to do so with a reasonable expectation of success. It is respectfully submitted that there is no basis in fact or law supporting the *prima facie* rejection of the claims. Moreover, if the *prima facie* is held to have a basis as set forth in the specification, *in arguendo*, then Applicants have provided a factual evidence as a basis for a rebuttal of the *prima facie* rejection. Hence, it is respectfully submitted that the independent claims are distinguishable over the prior art.

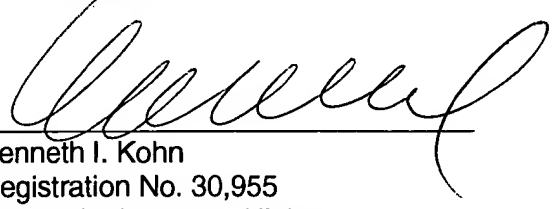
The remaining dependent claims not discussed above are ultimately dependent upon at least one of the independent claims discussed above. No prior art reference makes up for the deficiencies of that reference as applied against the independent claims as no prior reference discloses or suggests the invention as set forth in the independent claims, as discussed in detail above. Such a combination of references that derive the present invention can only be made through hind sight as no prior art reference discloses or even suggest the fusion protein of the present invention, as discussed in detail above.

In view of the above, the application is in condition for allowance which allowance is respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

KOHN & ASSOCIATES



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Dated: May 13, 2002

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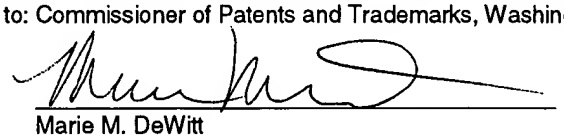

Marie M. DeWitt

VERSION SHOWING CHANGES

Beginning on pag 3, line 25 and ending on page 4, line 4, pleas am nd as follows:

In a preferred embodiment, the culture is inactivated by adding formalin (about 0.5% v/v final concentration). In another preferred embodiment, antigens of the invention are obtained from the supernatant or filtrate of an *E. rhusiopathiae* culture. A culture supernatant or filtrate, in a preferred embodiment, is concentrated about 10-fold and aluminum hydroxide gel (preferably REHYDRAGEL™) is added to the concentrated supernatant or filtrate at a final concentration of about 30% v/v to stabilize the antigen. In another preferred embodiment, a vaccine composition is formulated comprising the antigen and an adjuvant with the adjuvant comprising, for example, about 25% v/v of the vaccine composition. In another preferred embodiment, thimerosal (about 0.01% v/v final concentration) with EDTA (about 0.07% v/v final concentration) are added to the antigens as preservative. A preferred adjuvant, herein referred to as "No.1 Adjuvant", comprises about 2% v/v lecithin, about 18% v/v mineral oil, and about 8% v/v surfactant (e.g., about 5.6% v/v [Tween 80] TWEEN 80™ and about 2.4% v/v [Span 80] SPAN 80™), with the remaining volume being a saline solution (e.g., Dulbecco PBS). This adjuvant is described in U.S. Patent Application Serial No. 60/117,705, filed January 29, 1999, entitled "Adjuvants for Use in Vaccines", which is incorporated herein by reference.

Beginning on page 7, line 19 and ending on page 8, line 3, please amend as follows:

An antigen of the invention may be used in a vaccine composition to immunize an animal. In one embodiment, the vaccine composition contains an antigen of the invention and an adjuvant. In a preferred embodiment, an adjuvant useful for a vaccine composition of the invention comprises a lecithin, an oil, and a surfactant. A vaccine composition formulated with a preferred adjuvant contains a lecithin at from about 0.25% to about 12.5% v/v, more preferably from about 0.5% to about 5%, and most preferably from about 0.5% to about 1.25% v/v, an oil at from about 1% to about 23% v/v, more preferably from about 3.5% to about 10% and most preferably about 4.5%, and an amphiphilic surfactant at from about 1.5% to about 6% v/v, more preferably from about 1.5% to about 4% and most preferably about 2% v/v. Preferably the adjuvant has 2 amphiphilic surfactants, for example [Tween] TWEEN™ and [Span] SPAN™ surfactants, of which one predominantly in the aqueous phase (e.g., [Tween 80] TWEEN 80™) of the vaccine composition and one in the oil phase (e.g., [Span 80] SPAN 80™). Preferably, when [Tween 80] TWEEN 80™ and [Span 80] SPAN 80™ are used as surfactants, the concentration of [Tween 80] TWEEN 80™ is about 1½ to about 3 times as high as the concentration of [Span 80] SPAN 80™, preferably about 2 times. A preferred adjuvant contains an aqueous carrier solution,

for example, phosphate-buffered saline (PBS) (e.g., Dulbecco PBS). A lecithin and an oil suitable for an adjuvant for the vaccine compositions is a mixture of lecithin in DRAKEOL™ 5 Lt Mineral Oil. Lecithin may be obtained from Central Soya, Fort Wayne, Indiana. *See also* U.S. Patent No. 5,084,269, which discusses adjuvant compositions. [Tween] TWEEN™ and [Span] SPAN™ surfactants may be obtained from Van Waters and Rogers, Omaha, Nebraska.

Beginning on page 10, line 27 and ending on line 31, please amend as follows:

E. rhusiopathiae strain CN 3342 is cultured in medium containing Difco Proteose Peptone at a concentration of 2.75%, Difco Yeast Extract (0.55%), [Tween 80] TWEEN 80™ (0.2%), K_2HPO_4 (0.217%) and KH_2PO_4 (0.061%) in deionized water. The pH of the medium is adjusted to 7.2 with 5N NaOH. The medium is steam sterilized at a minimum of 122° C for 30 to 90 minutes. After autoclaving, sterile 50% dextrose solution is added to a final concentration of 3% w/v.

Beginning on page 12, line 18 and ending on line 27, please amend as follows:

The adjuvant used was No.1 Adjuvant. 1000 mL of No.1 Adjuvant were made from 200 mL filter sterilized lecithin-oil solution (10% lecithin in DRAKEOL™ mineral oil), autoclaved [Tween 80] TWEEN 80™ (56 mL) and [Span 80] SPAN 80™ (24 mL), and phosphate buffered saline (Dulbecco PPPBS) (720 mL). The lecithin-oil solution and [Span 80] SPAN 80™ were combined and mixed in a sterile tank for at least 1 hour at room temperature until emulsification was complete. The saline and [Tween 80] TWEEN 80™ were combined and mixed in a sterile tank for at least 1 hour at room temperature. The oil mixture was emulsified with the aqueous mixture using a Ross emulsifier. Emulsification was continued by recirculation until all of the adjuvant was added into the saline. The emulsion was then passed twice through a Gaulin press at room temperature. The adjuvant was stored at 2 to 8° C.

Beginning on page 15, line 7 and ending on line 30, please amend as follows:

Sows were bled 0 to 10 days prior to farrowing to determine their *E. rhusiopathiae* antibody titers. Piglets were randomized based on sows* serological titers and farrowing dates. Fifty eight (58) piglets derived from these sows/gilts were bled and vaccinated at approximately 3 weeks of age with one of the two experimental *E. rhusiopathiae* vaccines or the placebo (groups listed in Table 1). At approximately 4 weeks of age the piglets were weaned. At approximately 6 weeks of age the piglets were bled and revaccinated with the same vaccine. At approximately 2 months, 3 months, 4 months and 5 months of age all pigs were bled. At approximately 5½

months of age, all spare pigs were removed from the study. At approximately 6 months of age (20 weeks after second vaccination) pigs were bled and 40 pigs were challenged intramuscularly with 2 mL of a virulent culture of *E. rhusiopathiae* (237 mouse LD_{50}, 1.74 x 10^9 colony-forming units/mL) grown from a culture provided by the National Veterinary Services Laboratory. Animals were monitored for signs of clinical disease and by rectal temperature for 2 days prior to challenge, the day of challenge, and the 7 days following challenge. Any control animal meeting the criterion for elevated rectal temperature (40.9° C) was taken off study and treated with injectable penicillin. Any control animal that had clinical signs of disease, but did not meet the elevated rectal temperature criterion was humanely killed, necropsied, and samples of whole blood, spleen, and liver were cultured for *E. rhusiopathaie.* Any control animal that died was necropsied and samples of spleen and liver were cultured for *E. rhusiopathiae.* Any vaccinated animal meeting the criterion for elevated rectal temperature [($ 40.9° C)] (40.9° C) and/or clinical signs of disease was taken off study and treated with injectable penicillin. Any vaccinated animal dying following challenge was necropsied and samples of spleen and liver were cultured for *E. rhusiopathiae.* Antibody titers to *E. rhusiopathiae* were determined by ELISA described above and correlation of antibody titers with clinical protection was done.

IN THE CLAIMS:

19. (New) A method of using a stabilizing agent selected from the group consisting of metal hydroxide, a metal phosphate, an aluminum hydroxide gel, an aluminum phosphate gel, a calcium phosphate gel, a zinc hydroxide/calcium hydroxide gel, and an alum by adding the stabilizing agent to a supernatant of fluid fraction obtained from a *E. rhusiopathiae* culture.